

# BRITISH PHARMACEUTICAL CONFERENCE DUBLIN, 1956

## SCIENCE PAPERS AND DISCUSSIONS

(continued from page 804)

### ANALGESICS AND THEIR ANTAGONISTS: SOME STERIC AND CHEMICAL CONSIDERATIONS

PART I. THE DISSOCIATION CONSTANTS OF SOME TERTIARY AMINES AND  
SYNTHETIC ANALGESICS; THE CONFORMATIONS OF METHADONE-TYPE  
COMPOUNDS

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Received July 20, 1956

#### INTRODUCTION

THE features thought to confer analgesic activity<sup>1</sup> at least equal to that of pethidine may be summarised as follows:

1. A basic centre which is ionised, or partially ionised at physiological pH, so as to associate with an anionic site in the receptor surface. 2. A flat aromatic structure in the molecule to allow a strong collective van der Waals' force bonding to a flat portion of the receptor reinforcing the ionic bond mentioned in (1). 3. The basic group and the flat structure to be in almost the same plane; this to be accomplished by a completely rigid molecule or a slightly less rigid one held in the correct configuration by steric or other constraints. 4. A suitably orientated projecting hydrocarbon moiety to form, with the basic centre and flat aromatic structure, a three dimensional geometrical pattern (see XVIII).

The purpose of the present series of papers is to present a detailed study of the cationic portion of the molecules of analgesics (and analgesic antagonists) in so far as it influences the first and third features.

Small changes in the alkyl groups attached to the basic centre of an analgesic are known to lead to profound alterations in the degree and the character of the biological response. Compounds produced by the replacement of the *N*-Me group of morphine by *N*-Et, *N*-n-Pr and *N*-allyl groups exhibit a transition from active analgesics to less active compounds and then to anti-analgesics as the series is ascended<sup>2,3</sup>. In this paper the dissociation constants and the conformation of methadone type compounds are considered, in Part II the effect of the type of basic group upon the properties of the compounds and the degree of analgesic effects will be considered, and in Part III the effect of the type of basic group upon the character of the biological response will be discussed.

## ANALGESICS AND THEIR ANTAGONISTS. PART I

### *Dissociation Constants of Analgesics and Related Compounds*

The pK'a values of several series of methadone-type compounds were determined in water at 25° C. and ionic strength of approximately 0.013 M (Table III).

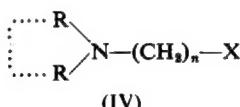
In Table I the reported analgesic activities and pK'a values of compounds of widely differing potencies are recorded, while in Table II the pK'a values of simpler amines are given.

### DISCUSSION

It is desirable to consider the observed  $\Delta pK_a$  values of the simpler amines of Table II before attempting to interpret those of the complex analgesics containing these basic groups. Since all the values quoted in the Table were not obtained using constant ionic strength of the medium, too much reliance cannot be placed upon minor differences. However, the consistent pattern upon changes of the various groups in the series indicates that the results may be used as the basis for generalisations.

The strength of an organic nitrogen base, as indicated by dissociation constants, is dependent upon the facility with which the lone pair electron cloud will attract and bind a solvated proton. Any effect which results in an increase in electron density in the lone pair orbital will increase the strength of the base. Any substituent exerting an electrical or steric effect to distort the orbital is considered to partially neutralise the electric charge around the nitrogen atom and be base weakening.

A substituent X may influence the basic strength of the tertiary amine (IV) by various mechanisms,



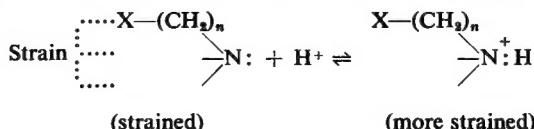
the observed effect being usually a complex combination of these.

(a) An inductive effect which is transmitted along the atoms of the chain may occur; it decreases rapidly with chain length.

(b) A direct electrostatic effect ("field effect") may operate through the solvent or free space between the substituent and the basic centre.

(c) The steric requirements of the substituent in proximity to the basic group may militate against the formation of the cation ( $\text{--}\overset{+}{\text{N}}\text{---H}$ ) which has larger steric requirements, due to solvation, than the corresponding unionised group ( $\text{--}\text{N}\text{:}$ ).

(d) The substituent will have a base weakening effect if there are greater steric interactions between the groups attached to the nitrogen in the 4-co-ordinated cation than in the 3-co-ordinated amine (B-strain)<sup>20,21</sup>.



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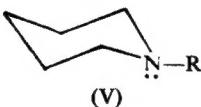
(e) The steric requirement of the substituent could result in greater difficulty of approach and increased facility of recession of a solvated proton. This is likely to be a relatively unimportant factor since it is known that the steric requirements of a proton are exceedingly small, e.g. the alkyl groups in 2:6-lutidine exert large steric effects sufficient to prevent combination with trimethyl borine and yet have no effect on the addition of a proton<sup>20</sup>.

(f) The above effects may be further complicated by alteration of groups R and their inclusion as a ring structure, with or without atoms or groups possessing dipoles.

The observed differences in dissociation constants in the simple compounds in Table II may be explained in terms of the above effects. The values indicate that *N*-ethyl compounds are stronger bases than the corresponding *N*-methyl compounds by about 0.3 to 0.4 pKa units, e.g., piperidines 10 and 9 ( $\Delta pK_a$  0.42), morpholines 13 and 12 ( $\Delta pK_a$  0.29), pyrrolidines 24 and 23 ( $\Delta pK_a$  0.38), trialkylamines 27 and 26 ( $\Delta pK_a$  0.40). This is attributed to the ethyl group, which has a larger +I effect than a methyl group, increasing the electron density on the nitrogen atom. Further increase in chain length produces no change, e.g., 2/3 and 4, and 10/11; the increase in inductive effect will be almost negligible and even this minor increase will be counter-balanced by the increased B-strain (with its base weakening effect) caused by increased chain length.

The fact that morpholino compounds are weaker bases than the corresponding piperidine analogues by about 2.65 pKa units is attributed to the inductive effect of the ring oxygen reducing the electron density on the nitrogen atom of the former compounds. The concordance of  $\Delta pK_a$  values of comparable compounds containing the two ring systems despite the wide variation of the *N*-alkyl groups supports this contention.

The dialkylamino-R compounds are slightly stronger bases than the corresponding piperidino compounds, e.g., 27/2 ( $\Delta pK_a$  0.33), 28/3 ( $\Delta pK_a$  0.17) (see later also). Six membered rings adopt a strain-free puckered conformation; it is difficult to account for the above difference in terms of strain in the ring favouring  $\text{>} \text{N:}$  at the expense of  $\text{>} \overset{+}{\text{N:}} \text{H}$ . An increase in B strain in the ring compound may occur but it seems more reasonable to explain the difference as follows. An *N*-alkyl piperidine



will adopt the chair conformation (V), and by analogy with cyclohexane, it would be predicted that the R group is equatorial since even a  $\text{CH}_3$  group has been shown to have a greater steric requirement than an electron pair. The approach of a proton in cation formation is therefore sterically controlled (towards axial lone pair), since the movement of the lone pair electrons to other positions would cause ring conformation change involving an increase in non-bonded interactions between the

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R group and the atoms of the ring. Such control will not operate in the analogous open chain compounds; cation formation will therefore be statistically more favoured in these as compared with the ring compounds.

The introduction of an  $\alpha$ -CH<sub>3</sub> group into a piperidine ring has a base strengthening effect, e.g., 11/3 ( $\Delta pK_a$  0.24) 10/2 ( $\Delta pK_a$  0.27). The +I effect of the CH<sub>3</sub> group will increase the electron density on the nitrogen atom; its bulk in the vicinity of this atom will operate against cation formation. The inductive effect is presumed to play the major role since the CH<sub>3</sub>-group will adopt an equatorial position and the rotation of the whole ring will result in the group keeping a fixed position from the N-atom lone pair electrons so that only a small steric effect will obtain.

The presence of a double bond  $\beta$  to the N atom has a base weakening effect due to the reduced electron density on this atom.

### *The dissociation constants of analgesics*

The pK'a values quoted in Table I are from the data of Farmilo and others<sup>13</sup>, who used aqueous ethanol as solvent in many of the determinations. Values measured in water are likely to be slightly different, but those of Table I indicate that there is no simple relation between dissociation constants and analgesic activities.

TABLE I  
DISSOCIATION CONSTANTS\* AND ACTIVITIES† OF VARIOUS ANALGESICS

Analgesic	pK'a	Approx. analgesic activities (Morphine = 100)
Morphine HCl . . . . .	8.05	100
Diacetylmorphine . . . . .	7.83	>100
Codeine phosphate . . . . .	8.22	10
Dihydromorphone HCl . . . . .	8.15	450
Metopon HCl . . . . .	8.08	1250
Levorphan tartrate . . . . .	8.18	>200
Nalorphine HCl . . . . .	7.83	—
Pethidine HCl . . . . .	8.72	20
$\alpha$ -Prodine HCl . . . . .	8.73	60–100
Methadone HCl . . . . .	8.25	100
Isomethadone HCl . . . . .	8.07	66
Phenadoxone . . . . .	6.89	>100
6-Piperidino-4:4-diphenylheptan-3-one . . . . .	6.8	100 or > 100

\* Dissociation constants are taken from ref. 13. † Activities (in rats or mice) are taken from refs. 5 to 12.

The values lie within the range of pK'a 7.8 to 8.9 (corresponding to about 86 to 98 per cent. ionisation as cations at physiological pH) with the exception of those of phenadoxone and its piperidino analogue. Titrations under aqueous conditions (see Part II) gave results for phenadoxone (pK'a 6.73) and a few of the analgesics in Table I in general agreement with the values obtained by Farmilo, but the piperidino analogue of phenadoxone was found to have a pK'a of 8.59 (Farmilo and others<sup>13</sup>, 6.8). It seems probable that the basic group must be ionised at physiological pH, to allow association with the anionic site of the receptor, but only partly so. It is known that ions penetrate membranes less readily than the corresponding neutral molecules due to their charge and relatively greater size (due to hydration)<sup>4,14</sup>. Unionised molecules may be necessary in the case of analgesics to allow rapid penetration of

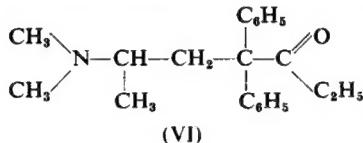
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membranes; the molecules after penetration to the biophase at the receptor site will then partially ionise as cations to a degree dependent upon their pKa values and the pH of the medium.

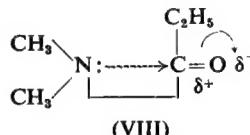
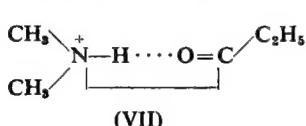
*The dissociation constants of methadone-type compounds*

The pK'a values of these analgesics will be affected by interactions of the basic centre with other groups in the molecule.

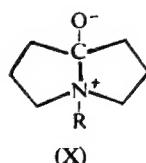
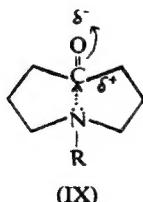
In a previous paper<sup>1</sup>, it was stated that the bulky groups attached to the quaternary carbon imparted a rigidity to the methadone molecule (VI).



The phenyl groups will occupy positions corresponding to the sides of a trihedral angle with the quaternary carbon at the apex. The nitrogen atom and carbonyl group will be held by electrostatic forces so that the conformation of the molecule is such that one phenyl ring and the nitrogen atom are capable of alignment with the flat surface and anionic site respectively of the proposed analgesic receptor surface (XVIII). It was suggested that hydrogen bonding of type VII might be the mechanism by which the nitrogen group (as a cation) and the carbonyl group are held in close proximity.

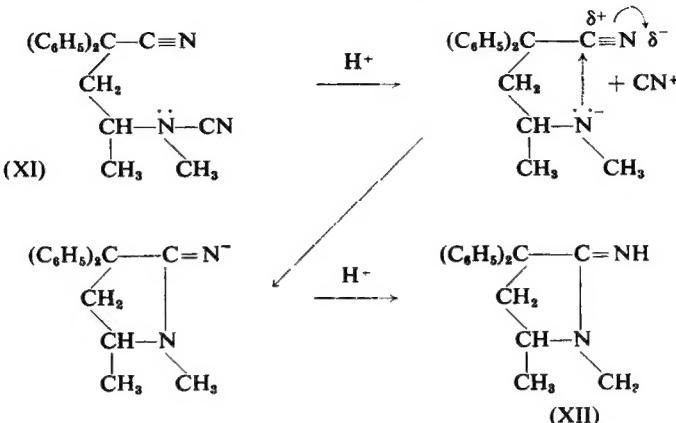


An alternative mechanism may be formulated (VIII), in which the lone pair orbital of the nitrogen atom interacts with the electropositive carbonyl carbon atom. Such a mechanism would be analogous to the transannular interaction<sup>22</sup> between amino nitrogen and carbonyl group in compounds of type IX. These have been shown to exist in certain conditions chiefly in the form X<sup>22</sup>.



Certain chemical and physical data<sup>23</sup> indicated that this type of interaction rather than hydrogen bonding constituted the mechanism of the attractive forces. Acid hydrolysis of XI yielded the imino-pyrrolidine (XII); the mechanism shown seems probable (see also Wilson<sup>24,25</sup>).

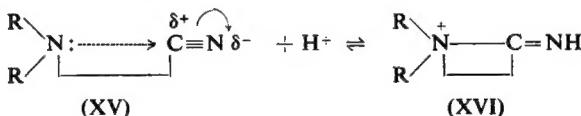
## ANALGESICS AND THEIR ANTAGONISTS. PART I



The infra-red spectrum of XIII exhibited a characteristic nitrile absorption in the region of  $2250 \text{ cm}^{-1}$ , whereas basic compounds of type



XIV showed only very weak nitrile absorption in this region, and in their salts the characteristic absorption peak was lacking. No evidence of  $\text{C}=\text{NH}$  absorption was found. It is presumed that nitrile-amino interactions occur but are not sufficiently powerful to result in the formation of XVI from XV upon salt formation.



The dissociation constants of several series of methadone-type compounds were determined (Table III) in an attempt to provide information on the above interactions under aqueous conditions.

The replacement of the H atom ( $\text{R}' = \text{H}$ ) by the cyano group ( $\text{R}' = \text{CN}$ ) in methadone type compounds (I) and (II) has a base weakening effect ( $\Delta pK_a$  values A, 0.89 and 1.07; D, 1.09 and 1.17; B, 1.14 and 0.8) (Table III). A smaller base weakening effect results upon the introduction of the ketonic group ( $\text{R}' = \text{COC}_2\text{H}_5$ ) ( $\Delta pK_a$  values A, 0.10 and 0.22; D, 0.19 and 0.49; B, 0.25 and 0.17). Since both the cyano and ketonic groups are electronegative in character, the observed differences may be attributed to the inductive effect along the chain separating these groups from the basic centre, or a field effect operating through space or solvent if the interacting groups are in close proximity. Until recently it has been impossible to assess the relative importance of the two modes of transmission in a particular compound. Grob and others<sup>26</sup> have now presented

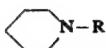
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evidence, from considerations of the dissociation constants of certain betaine hydrochlorides, to show that the so-called general inductive effect appears as a function of the direct distance between electrostatically interacting groups and the dielectric constant of the intervening medium; this can be a chain of atoms, solvent or empty space according to the geometry of the system. The base weakening effect of a cyano or keto group in methadone type compounds would be expected to have little effect upon the basic centre if maximum group separation occurred. The results indicate that the molecules assume a conformation in which the cyano (or keto) group and basic centre are in close proximity.

The base weakening effects also indicate that the interactions are of the type shown in VIII rather than VII since the latter would be expected

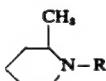
TABLE II  
pK'a VALUES FOR VARIOUS TERTIARY AMINES  
TEMPERATURE 25° C.; SOLVENT WATER

A



	R	pK'a
1	CH <sub>3</sub>	10.15
2	C <sub>2</sub> H <sub>5</sub> (b)	10.41
3	n-C <sub>3</sub> H <sub>7</sub> (c)	10.48
4	n-C <sub>4</sub> H <sub>9</sub> (c)	10.49
5	-CH <sub>2</sub> CH = CH <sub>2</sub> (d)	9.68
6	-(CH <sub>2</sub> ) <sub>2</sub> N-	6.25 9.47
7	-(CH <sub>2</sub> ) <sub>3</sub> N-	7.9 9.95
8	-CH <sub>2</sub> CH <sub>2</sub> OH-CH <sub>2</sub> -N-	7.47 9.48

E



	R	pK'a
9	CH <sub>3</sub> (c)	10.26
10	C <sub>2</sub> H <sub>5</sub> (b)	10.68
11	n-C <sub>4</sub> H <sub>9</sub> (b)	10.72

B



	R	pK'a	ΔpKa A-B
12	CH <sub>3</sub> (d)	7.41	+ 2.74
13	C <sub>2</sub> H <sub>5</sub> (d)	7.70	+ 2.71
14	-CH <sub>2</sub> -CH=CH <sub>2</sub> (d)	7.05	+ 2.63
15	-(CH <sub>2</sub> ) <sub>2</sub> N-	3.63 6.65	+ 2.62 + 2.82
16	-(CH <sub>2</sub> ) <sub>3</sub> N-	5.25 7.25	+ 2.65 + 2.7
17	-CH <sub>2</sub> CH <sub>2</sub> OH-CH <sub>2</sub> -N-	5.00 6.98	+ 2.47 + 2.50

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C



	R	pK'a	$\Delta pK_a$ A-C
18	CH <sub>3</sub> (a)	10.14	+ 0.01
19	n-C <sub>4</sub> H <sub>9</sub>	10.36	+ 0.13
20	-(CH <sub>2</sub> ) <sub>2</sub> N-	6.3 9.47	- 0.05 0.0
21	-(CH <sub>2</sub> ) <sub>2</sub> N-	8.03 10.04	- 0.13 - 0.09
22	-(CH <sub>2</sub> )CH <sub>2</sub> OH-CH <sub>2</sub> N-	7.75 9.73	- 0.28 - 0.25

F



	R	pK'a	$\Delta pK_a$ E-F
23	CH <sub>3</sub> (c)	10.26	0.0
24	C <sub>2</sub> H <sub>5</sub> (c)	10.64	+ 0.04
25	n-C <sub>4</sub> H <sub>9</sub> (c)	10.69	+ 0.03

D



	R'	R	pK'a	$\Delta pK_a$ A-D
26	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> (b)	10.34	- 0.19
27	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub> (b)	10.74	- 0.33
28	n-C <sub>4</sub> H <sub>9</sub>	n-C <sub>4</sub> H <sub>9</sub> (b)	10.65	- 0.17
29	C <sub>4</sub> H <sub>9</sub>	-(CH <sub>2</sub> ) <sub>2</sub> N(C <sub>4</sub> H <sub>9</sub> ) <sub>2</sub> (e)	6.18 9.55	+ 0.07 - 0.08
30	C <sub>4</sub> H <sub>9</sub>	-(CH <sub>2</sub> ) <sub>2</sub> N(C <sub>4</sub> H <sub>9</sub> ) <sub>2</sub> (e)	8.2 10.18	- 0.30 - 0.23
31	C <sub>4</sub> H <sub>9</sub>	-(CH <sub>2</sub> )CH <sub>2</sub> OH-CH <sub>2</sub> N(C <sub>4</sub> H <sub>9</sub> ) <sub>2</sub> (e)	7.74 9.80	- 0.27 - 0.32

(a) See ref. 15. (b) See ref. 16. (c) See ref. 17. (d) See ref. 18. (e) see ref 19.

to have a base strengthening effect (e.g., the fact that basic groups with proximate rather than distal COO<sup>-</sup> groups are the stronger bases of corresponding pairs, is attributed to hydrogen bonding COO<sup>-</sup>...H-N<sup>+</sup> in the former compounds<sup>27</sup>).

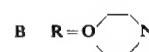
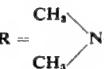
The  $\Delta pK_a$  values between the piperidino and corresponding morpholino compounds in these methadone type bases (Table III,  $\Delta pK_a$  A - B) are much lower than those for the simpler bases in Table II. This decreased base weakening effect of the morpholino oxygen in these methadone compounds is attributed to the competing electron attractive forces of the substituent in the N-alkyl chain which reduce the  $-I$  contribution of the oxygen atom.

The presence of a CH<sub>3</sub> group on the  $\alpha$ -carbon of the N-alkyl chain has a base weakening effect in these analgesically active ketones (the  $\Delta pK_a$  values 33/36, 46/49 and 40/43 are 0.28, 0.24 and 0.27 respectively). Consideration of molecular models in the conformation with carbonyl and

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nitrogen function in close proximity indicates that the  $\text{CH}_3$  group will impose a steric limitation in the vicinity of the N atom and so favour the neutral molecule rather than the larger cation. B strain will also be increased by the introduction of this group. These two base weakening effects will be more important in these compounds than the  $+I$  base strengthening contribution of the group. It is to be noted that the contribution of the methyl group is different from the base strengthening effect of such a group on the  $\alpha$ -carbon atom of simple *N*-alkylated heterocyclic rings (e.g., *N*-alkyl-piperidines) (Table II). A  $\text{CH}_3$  group on the  $\beta$ -carbon atom of the chain (see III) of normethadone would be expected to have even a greater base weakening effect if the above interpretations are correct. Isomethadone nitrile (IIID) ( $\text{pK}_a$  7.9) and its piperidino analogue ( $\text{pK}_a$  7.54) are weaker bases than their respective *nor*-compounds by 0.41 and 0.53  $\text{pK}_a$  units respectively.

TABLE III  
DISSOCIATION CONSTANTS ( $\text{pK}'_a$ ) OF METHADONE-TYPE ANALGESICS AND RELATED COMPOUNDS  
TEMPERATURE  $25^\circ \text{ C.}$ ; SOLVENT WATER

$\begin{array}{c} \text{C}_6\text{H}_5 \\   \\ \text{R}-\text{CH}_2-\text{CH}_2-\text{C}-\text{R}' \\   \\ \text{C}_6\text{H}_5 \end{array} \quad (\text{I})$														
A   R = 					B   R = 					D   R = 				
Compound No.	R'	pK'a	Compound No.	R'	Compound No.	R'	pK'a	$\Delta\text{pK}_a$ A-B	Compound No.	R'	pK'a	$\Delta\text{pK}_a$ A-D		
32	H	8.96	39	H	7.25	+ 1.71	45	H	9.40	- 0.44				
33	$-\text{COC}_2\text{H}_5$	8.86	40	$-\text{COC}_2\text{H}_5$	7.00	+ 1.86	46	$-\text{COC}_2\text{H}_5$	9.23	- 0.37				
34	$-\text{CN}$	8.07	41	$-\text{CN}$	6.09	+ 1.98	47	$-\text{CN}$	8.31	- 0.24				

$\begin{array}{c} \text{C}_6\text{H}_5 \\   \\ \text{R}-\text{CH}-\text{CH}_2-\text{C}-\text{R}' \\   \\ \text{CH}_3 \qquad \text{C}_6\text{H}_5 \end{array} \quad (\text{II})$														
Com-					Com-					Com-				
Compound No.	R'	pK'a	Compound No.	R'	Compound No.	R'	pK'a	$\Delta\text{pK}_a$ A-B	Compound No.	R'	pK'a	$\Delta\text{pK}_a$ A-D		
35	H	8.80	42	H	6.90	+ 1.90	48	H	9.48	- 0.68				
36	$-\text{COC}_2\text{H}_5$	8.58	43	$-\text{COC}_2\text{H}_5$	6.73	+ 1.83	49	$-\text{COC}_2\text{H}_5$	8.99	- 0.41				
37	$-\text{CN}$	7.73	44	$-\text{CN}$	6.10	+ 1.63	50	$-\text{CN}$	8.31	- 0.58				

$\begin{array}{c} \text{C}_6\text{H}_5 \\   \\ \text{R}-\text{CH}_2-\text{CH}-\text{C}-\text{R}' \\   \\ \text{CH}_3 \qquad \text{C}_6\text{H}_5 \end{array} \quad (\text{III})$														
Com-					Com-					Com-				
Compound No.	R'	pK'a	Compound No.	R'	Compound No.	R'	pK'a	$\Delta\text{pK}_a$ A-B	Compound No.	R'	pK'a	$\Delta\text{pK}_a$ A-D		
38	$-\text{CN}$	7.54							51	$-\text{CN}$	7.90	- 0.36		

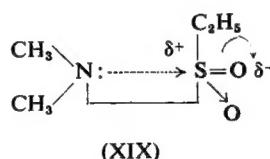
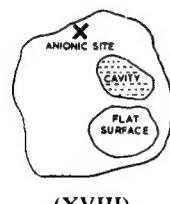
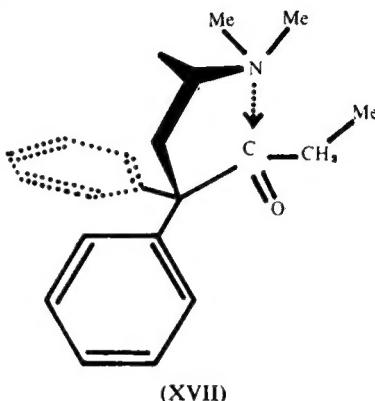
## ANALGESICS AND THEIR ANTAGONISTS. PART I

As in simpler compounds (Table II), the piperidino compounds of Table III are weaker bases than their dimethylamino analogues by about 0·4 units (see Table III,  $\Delta pK_a$  A — D).

The infra-red and the dissociation constants data, as well as the chemical data briefly reported in the paper, all indicate a mutual interaction of basic and nitrile (or carbonyl) groups caused by their close proximity in the molecular conformation adopted, and the probability of the attractive forces being N-C<sub>CN</sub> and N-C<sub>CO</sub> interactions (see VIII).

A preferred conformation of methadone in aqueous solution may be regarded as that portrayed in XVII: association with the proposed analgesic receptor site (XVIII) is therefore facilitated.

The morpholino and piperidino analogues of methadone and the



corresponding "iso" (III; R = COC<sub>2</sub>H<sub>5</sub>) and "nor" (I; R = COC<sub>2</sub>H<sub>5</sub>) compounds may be regarded as adopting similar conformations. Replacement of the ethyl ketone group of methadone by the ethyl sulphone group gives an active analgesic<sup>28</sup>. It is reasonable to assume that this compound also has a similar conformation, the attractive forces between basic and sulphone groups being as shown in XIX.

### EXPERIMENTAL

All m.pts. are uncorrected.

#### *Preparation (or source) of compounds*

(The compound numbers correspond with those of Table III.)

The m.pts. of the bases or salts used in the measurement of dissociation constants are recorded in Table IV.

TABLE IV

THE MELTING POINTS OF THE BASES OR SALTS USED IN THE MEASUREMENT OF DISSOCIATION CONSTANTS

Compd. No.	Base or salt	M.pt. ° C.	Compd. No.	Base or salt	M.pt. ° C.	Compd. No.	Base or salt	M.pt. ° C.
32	HCl	211 to 212	39	HCl	207 to 208	45	HCl	144 to 145
33	HCl	175 to 176	40	base	115 to 116	46	HCl	173·5 to 175
34	base	70	41	base	81 to 82	47	HCl	200
35	HCl	214	42	HCl	198 to 199	48	HCl	151 to 153
36	HCl	117 to 120·5	43	(-)base	60 to 61	49	HCl	233 to 234
37	HCl	203	44	base	106	50	(-)base	100 to 101
38	HBr	249				51	HBr	223

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3-Morpholino-1:1-diphenylpropyl cyanide (Compd. No. 41), m.pt. 81 to 82°C., 3-piperidino-1:1-diphenylpropyl cyanide (Compd. No. 34), m.pt. 70°C., and 3-dimethylamino-1:1-diphenylpropyl cyanide hydrochloride (Compd. No. 47), m.pt. 200°C. were prepared by the methods of Dupré and others<sup>29</sup> who quoted m.p.s. of 82°C., 70 to 71°C. and 200 to 201°C. respectively for these compounds. Compounds No. 39 and 40 (see ref. 30). Compounds No. 33, 43, 44 and 46 (kindly supplied by Dr. J. Elks). Compounds No. 48 and 50 (see refs. 28 and 31). Compounds No. 36, 37 and 38 (kindly supplied by Dr. G. E. Foster). Compound No. 49 (Burroughs Wellcome Ltd.). Compounds 32, 35, 42 and 45 were prepared by the following general method. The appropriate 3-amino-1:1-diphenylpropyl cyanides or 3-amino-1:1-diphenylbutyl amides were refluxed with equal weights of sodamide in dry toluene for 16 hours. The excess of sodamide was filtered off, the solvent removed under reduced pressure and the resultant oil converted to the hydrochloride which was recrystallised from ethanol-ether : 3-morpholino-1:1-diphenylbutane hydrochloride (Compd. No. 42), m.pt. 198 to 199°C. (Bochmühl and Ehrhart<sup>10</sup> quote m.pt. 198 to 199°C.), 3-piperidino-1:1-diphenylbutane hydrochloride (Compd. No. 35), m.pt. 214°C. (Bochmühl and Ehrhart<sup>10</sup> quote m.pt. 214 to 215°C.), 3-piperidino-1:1-diphenylpropane hydrochloride (Compd. No. 32), m.pt. 214.5 to 215°C. (Found: C, 75.95; H, 8.0 per cent., equiv. wt. 313.  $C_{20}H_{26}NCl$  requires C, 76.0; H, 8.3 per cent., equiv. wt. 315.5), 3-dimethylamino-1:1-diphenylpropane hydrochloride, m.pt. 144 to 145°C. (Found: C, 73.5; H, 8.0 per cent., equiv. wt. 278.  $C_{17}H_{22}NCl$  requires C, 74.0; H, 8.0 per cent., equiv. wt. 275.5.)

Compound 51. Prepared by recrystallisation of the hydrobromides of the mixed nitriles obtained in the methadone synthesis; 3-dimethylamino-2-methyl-1:1-diphenylpropyl cyanide hydrobromide crystallised from ethanol-ether as colourless prisms m.pt. 223°C. (Walton and Ofner<sup>32</sup> quote m.pt. 223 to 224°C.).

*Measurement of dissociation constants*

The dissociation constants recorded in Table III were measured in water at 25°C. by the method described in Part II of this series.

SUMMARY

1. The dissociation constants of certain *N*-alkylated piperidines, morpholines, pyrrolidines and dialkylamines are discussed in terms of combined electrical and steric effects.
2. Interactions of the basic group with other groups in methadone-type molecules are briefly outlined.
3. Dissociation constants of several series of methadone-type compounds are recorded; consideration is given to the effect upon these values of the conformation of the molecules and combined electrical and steric effects.
4. Methadone type molecules are shown to adopt a conformation which permits their ready association with the "analgesic receptor site".

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The author wishes to express his thanks to Dr. J. Elks (Glaxo Laboratories Ltd.) and Dr. G. E. Foster (Burroughs Wellcome and Co.) for supplying certain samples used in this investigation.

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